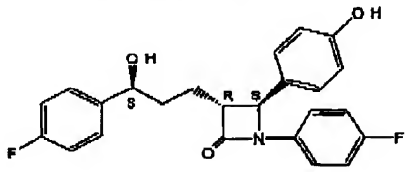
Exhibit A

ZETIA™

(EZETIMIBE)
TABLETS

DESCRIPTION

ZETIA (ezetimibe) is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$, its molecular weight is 409.4 and its structural formula is:



Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature. ZETIA is available as a tablet for oral administration containing 10 mg of ezetimibe and the following inactive ingredients: croscarmellose sodium NF, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, povidone USP, and sodium lauryl sulfate NF.

CLINICAL PHARMACOLOGY

Background

Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B), the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of high density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

ZETIA reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia. Administration of ZETIA with an HMG-CoA reductase inhibitor is effective in improving serum total-C, LDL-C, Apo B, TG, and HDL-C beyond either treatment alone. The effects of ezetimibe given either alone or in addition to an HMG-CoA reductase inhibitor on cardiovascular morbidity and mortality have not been established.

Mode of Action

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. In a 2-week clinical study in 18 hypercholesterolemic patients, ZETIA inhibited intestinal cholesterol absorption by 54%, compared with placebo. ZETIA had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E (in a study of 113 patients), and did not impair adrenocortical steroid hormone production (in a study of 118 patients).

The cholesterol content of the liver is derived predominantly from three sources. The liver can synthesize cholesterol, take up cholesterol from the blood from circulating lipoproteins, or take up cholesterol absorbed by the small intestine. Intestinal cholesterol is derived primarily from cholesterol excreted in the bile and from dietary cholesterol.

Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds (HMG-CoA reductase inhibitors, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols).

Ezetimibe does not inhibit cholesterol synthesis in the liver, or increase bile acid excretion. Instead, ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG-CoA reductase inhibitors (see CLINICAL STUDIES).

Pharmacokinetics

Absorption

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10-mg dose of ZETIA to fasted adults, mean ezetimibe peak plasma concentrations (C_{max}) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (T_{max}). Ezetimibe-glucuronide mean C_{max} values of 45 to 71 ng/mL were achieved between 1 and 2 hours (T_{max}). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection. Ezetimibe has variable bioavailability; the coefficient of variation, based on inter-subject variability, was 35 to 50% for AUC values.

Effect of Food on Oral Absorption

Concomitant food administration (high fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ZETIA 10-mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high fat meals. ZETIA can be administered with or without food.

ZETIA™ (ezetimibe)

Distribution

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Metabolism and Excretion

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary and renal excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Special Populations

Geriatric Patients

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

Pediatric Patients

In a multiple dose study with ezetimibe given 10 mg once daily for 7 days, the absorption and metabolism of ezetimibe were similar in adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Gender

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Race

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians. There were too few patients in other races or ethnic groups to permit further pharmacokinetic comparisons.

Hepatic Insufficiency

After a single 10-mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe were increased approximately 3-4 fold and 5-6 fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, the mean AUC values for total ezetimibe and ezetimibe were increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients (see CONTRAINDICATIONS and PRECAUTIONS, *Hepatic Insufficiency*).

Renal Insufficiency

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73 m²), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

Drug Interactions (See also PRECAUTIONS, *Drug Interactions*)

ZETIA had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" study of twelve healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

Warfarin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males.

Digoxin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of digoxin and the ECG parameters (HR, PR, QT, and QTc intervals) in a study of twelve healthy adult males.

Gemfibrozil: In a study of twelve healthy adult males, concomitant administration of gemfibrozil (600 mg twice daily) significantly increased the oral bioavailability of total ezetimibe by a factor of 1.7. Ezetimibe (10 mg once daily) did not significantly affect the bioavailability of gemfibrozil.

Oral Contraceptives: Co-administration of ezetimibe (10 mg once daily) with oral contraceptives had no significant effect on the bioavailability of ethinyl estradiol or levonorgestrel in a study of eighteen healthy adult females.

Cimetidine: Multiple doses of cimetidine (400 mg twice daily) had no significant effect on the oral bioavailability of ezetimibe and total ezetimibe in a study of twelve healthy adults.

Antacids: In a study of twelve healthy adults, a single dose of antacid (Suprelox™ 20 mL) administration had no significant effect on the oral bioavailability of total ezetimibe, ezetimibe-glucuronide, or ezetimibe based on AUC values. The C_{max} value of total ezetimibe was decreased by 30%.

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Glipizide: In a study of twelve healthy adult males, steady-state levels of ezetimibe (10 mg once daily) had no significant effect on the pharmacokinetics and pharmacodynamics of glipizide. A single dose of glipizide (10 mg) had no significant effect on the exposure to total ezetimibe or ezetimibe.

HMG-CoA reductase inhibitors: In studies of healthy hypercholesterolemic (LDL-C ≥130 mg/dl) adult subjects, concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of either lovastatin, simvastatin, pravastatin, atorvastatin, or fluvastatin. No significant effect on the bioavailability of total ezetimibe and ezetimibe was demonstrated by either lovastatin (20 mg once daily), pravastatin (20 mg once daily), atorvastatin (10 mg once daily), or fluvastatin (20 mg once daily).

Fenofibrate: In a study of thirty-two healthy hypercholesterolemic (LDL-C ≥130 mg/dl) adult subjects, concomitant fenofibrate (200 mg once daily) administration increased the mean C_{ss} and AUC values of total ezetimibe approximately 54% and 48%, respectively. Pharmacokinetics of fenofibrate were not significantly affected by ezetimibe (10 mg once daily).

Cholestyramine: In a study of forty healthy hypercholesterolemic (LDL-C ≥130 mg/dl) adult subjects, concomitant cholestyramine (4 g twice daily) administration decreased the mean AUC values of total ezetimibe and ezetimibe approximately 55% and 60%, respectively.

ANIMAL PHARMACOLOGY

The hypocholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and mouse models of human cholesterol metabolism. Ezetimibe was found to have an ED_{50} value of 0.5 µg/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED_{50} values in dogs, rats, and mice were 7, 30, and 700 µg/kg/day, respectively. These results are consistent with ZETIA being a potent cholesterol absorption inhibitor.

In a rat model, where the glucuronide metabolite of ezetimibe (SCH 60663) was administered intraduodenally, the metabolite was as potent as the parent compound (SCH 58235) in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03-300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3-5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

A series of acute preclinical studies was performed to determine the selectivity of ZETIA for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of C14 cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethyl estradiol, or the fat-soluble vitamins A and D.

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with HMG-CoA reductase inhibitors (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

CLINICAL STUDIES

Primary Hypercholesterolemia

ZETIA reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

ZETIA is effective in patients with hypercholesterolemia, in men and women, in younger and older patients, alone or administered with an HMG-CoA reductase inhibitor. Experience in pediatric and adolescent patients (ages 9 to 17) has been limited to patients with homozygous familial hypercholesterolemia (HoFH) or sitosterolemia.

Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of ZETIA.

Monotherapy

In two, multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ZETIA significantly lowered total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo (see Table 1). Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

Table 1
Response to ZETIA in Patients with Primary Hypercholesterolemia
(Mean† % Change from Untreated Baseline‡)

	Treatment group	N	Total-C	LDL-C	Apo B	TG*	HDL-C
Study 1*	Placebo	205	+1	+1	-1	-1	-1
	Ezetimibe	982	-12	-18	-15	+7	+1
Study 2*	Placebo	226	+1	+1	-1	+2	-2
	Ezetimibe	666	-12	-19	-16	-9	+1
Pooled Data* (Studies 1 & 2)	Placebo	431	0	+1	-2	0	-2
	Ezetimibe	1288	-13	-18	-16	-8	+1

†For triglycerides, median % change from baseline
‡Baseline = on no lipid-lowering drug
*ZETIA significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo.

Combination with HMG-CoA Reductase Inhibitors

ZETIA Added to On-going HMG-CoA Reductase Inhibitor Therapy

In a multicenter, double-blind, placebo-controlled, 8-week study, 769 patients with primary hypercholesterolemia, known coronary heart disease or multiple cardiovascular risk factors who were already receiving HMG-CoA reductase inhibitor monotherapy, but who had not met their NCEP ATP II target LDL-C goal were randomized to receive

either ZETIA or placebo in addition to their on-going HMG-CoA reductase inhibitor therapy.

ZETIA, added to on-going HMG-CoA reductase inhibitor therapy, significantly lowered total-C, LDL-C, Apo B, and TG, and increased HDL-C compared with an HMG-CoA reductase inhibitor administered alone (see Table 2). LDL-C reductions induced by ZETIA were generally consistent across all HMG-CoA reductase inhibitors.

Table 2
Response to Addition of ZETIA to On-going HMG-CoA Reductase Inhibitor Therapy[a] in Patients with Hypercholesterolemia (Mean[b] % Change from Treated Baseline[c])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[b]	HDL-C
On-going HMG-CoA reductase inhibitor +Placebo[d]	390	-2	-4	-3	-3	+1
On-going HMG-CoA reductase inhibitor +ZETIA[d]	379	-17	-25	-19	-14	+3

[a] Patients receiving each HMG-CoA reductase inhibitor: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)
[b] For triglycerides, median % change from baseline
[c] Baseline - on an HMG-CoA reductase inhibitor alone.
[d] ZETIA + HMG-CoA reductase inhibitor significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to HMG-CoA reductase inhibitor alone.

ZETIA Initiated Concurrently with an HMG-CoA Reductase Inhibitor

In four, multicenter, double-blind, placebo-controlled, 12-week trials, in 2382 hypercholesterolemic patients, ZETIA or placebo was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin.

When all patients receiving ZETIA with an HMG-CoA reductase inhibitor were compared to all those receiving the corresponding HMG-CoA reductase inhibitor alone, ZETIA significantly lowered total-C, LDL-C, Apo B, and TG, and, with the exception of pravastatin, increased HDL-C compared to the HMG-CoA reductase inhibitor administered alone. LDL-C reductions induced by ZETIA were generally consistent across all HMG-CoA reductase inhibitors. (See footnote c, Tables 3 to 6.)

Table 3
Response to ZETIA and Atorvastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	60	+4	+4	+3	-6	+4
ZETIA	65	-14	-20	-15	-5	+4
Atorvastatin 10 mg	60	-26	-37	-28	-21	+6
ZETIA + Atorvastatin 10 mg	65	-38	-53	-43	-31	+9
Atorvastatin 20 mg	60	-30	-42	-34	-23	+4
ZETIA + Atorvastatin 20 mg	62	-39	-54	-44	-30	+8
Atorvastatin 40 mg	66	-32	-45	-37	-24	+4
ZETIA + Atorvastatin 40 mg	65	-42	-56	-45	-34	+5
Atorvastatin 80 mg	62	-40	-54	-46	-31	+3
ZETIA + Atorvastatin 80 mg	63	-46	-61	-50	-40	+7
Pooled data (All Atorvastatin Doses)[c]	248	-32	-44	-36	-24	+4
Pooled data (All ZETIA + Atorvastatin Doses)[c]	255	-41	-56	-45	-33	+7

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of atorvastatin pooled (10-80 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of atorvastatin pooled (10-80 mg).

Table 4
Response to ZETIA and Simvastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	70	-1	-1	0	+2	+1
ZETIA	61	-13	-19	-14	-11	+5
Simvastatin 10 mg	70	-18	-27	-21	-14	+8
ZETIA + Simvastatin 10 mg	67	-32	-46	-35	-26	+9
Simvastatin 20 mg	61	-26	-36	-29	-18	+6
ZETIA + Simvastatin 20 mg	69	-33	-46	-36	-25	+9
Simvastatin 40 mg	65	-27	-38	-32	-24	+6
ZETIA + Simvastatin 40 mg	73	-40	-56	-45	-32	+11
Simvastatin 80 mg	67	-32	-45	-37	-23	+8
ZETIA + Simvastatin 80 mg	65	-41	-58	-47	-31	+8
Pooled data (All Simvastatin Doses)[c]	263	-26	-36	-30	-20	+7
Pooled data (All ZETIA + Simvastatin Doses)[c]	274	-37	-51	-41	-29	+9

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of simvastatin pooled (10-80 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of simvastatin pooled (10-80 mg).

Table 5
Response to ZETIA and Pravastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	65	0	-1	-2	-1	+2
ZETIA	64	-13	-20	-15	-5	+4
Pravastatin 10 mg	66	-15	-21	-16	-14	+6
ZETIA + Pravastatin 10 mg	71	-24	-34	-27	-23	+8
Pravastatin 20 mg	69	-15	-23	-18	-8	+8
ZETIA + Pravastatin 20 mg	66	-27	-40	-31	-21	+8
Pravastatin 40 mg	70	-22	-31	-26	-19	+6
ZETIA + Pravastatin 40 mg	67	-30	-42	-32	-21	+8
Pooled data (All Pravastatin Doses)[c]	205	-17	-25	-20	-14	+7
Pooled data (All ZETIA + Pravastatin Doses)[c]	204	-27	-39	-30	-21	+8

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of pravastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and TG compared to all doses of pravastatin pooled (10-40 mg).

Table 6
Response to ZETIA and Lovastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	64	+1	0	+1	+6	0
ZETIA	72	-13	-19	-14	-5	+5
Lovastatin 10 mg	73	-15	-20	-17	-11	+5
ZETIA + Lovastatin 10 mg	65	-24	-34	-27	-19	+9
Lovastatin 20 mg	74	-19	-26	-21	-12	+3
ZETIA + Lovastatin 20 mg	62	-29	-41	-34	-27	+9
Lovastatin 40 mg	73	-21	-30	-25	-15	+5
ZETIA + Lovastatin 40 mg	65	-33	-46	-38	-27	+9
Pooled data (All Lovastatin Doses)[c]	220	-18	-25	-21	-12	+4
Pooled data (All ZETIA + Lovastatin Doses)[c]	192	-29	-40	-33	-25	+9

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ZETIA + all doses of lovastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of lovastatin pooled (10-40 mg).

Homozygous Familial Hypercholesterolemia (HoFH)

A study was conducted to assess the efficacy of ZETIA in the treatment of HoFH. This double-blind, randomized, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40 mg). Patients were randomized to one of three treatment groups, atorvastatin or simvastatin (80 mg), ZETIA administered with atorvastatin or simvastatin (40 mg), or ZETIA administered with atorvastatin or simvastatin (80 mg). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine (see PRECAUTIONS), ezetimibe was dosed at least 4 hours before or after administration of resins. Mean baseline LDL-C was 341 mg/dL in those patients randomized to atorvastatin 80 mg or simvastatin 80 mg alone and 316 mg/dL in the group randomized to ZETIA plus atorvastatin 40 or 80 mg or simvastatin 40 or 80 mg. ZETIA, administered with atorvastatin or simvastatin (40 and 80 mg statin groups, pooled), significantly reduced LDL-C (21%) compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg (7%). In those treated with ZETIA plus 80 mg atorvastatin or with ZETIA plus 80 mg simvastatin, LDL-C was reduced by 27%.

Homozygous Sitosterolemia (Phytosterolemia)

A study was conducted to assess the efficacy of ZETIA in the treatment of homozygous sitosterolemia. In this multicenter, double-blind, placebo-controlled, 8-week trial, 37 patients with homozygous sitosterolemia with elevated plasma sitosterol levels (>5 mg/dL) on their current therapeutic regimen (diet, bile-acid-binding resins, HMG-CoA reductase inhibitors, ileal bypass surgery and/or LDL apheresis), were randomized to receive ZETIA (n=30) or placebo (n=7). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine (see PRECAUTIONS), ezetimibe was dosed at least 2 hours before or 4 hours after resins were administered. Excluding the one subject receiving LDL-apheresis, ZETIA significantly lowered plasma sitosterol and campesterol, by 21% and 24% from baseline, respectively. In contrast, patients who received placebo had increases in sitosterol and campesterol of 4% and 3% from baseline, respectively. For patients treated with ZETIA, mean plasma levels of plant sterols were reduced progressively over the course of the study. The effects of reducing plasma sitosterol and campesterol on reducing the risks of cardiovascular morbidity and mortality have not been established.

Reductions in sitosterol and campesterol were consistent between patients taking ZETIA concomitantly with bile acid sequestrants (n=8) and patients not on concomitant bile acid sequestrant therapy (n=21).

INDICATIONS AND USAGE

Primary Hypercholesterolemia

Monotherapy

ZETIA, administered alone is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Combination therapy with HMG-CoA reductase inhibitors

ZETIA, administered in combination with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Homozygous Familial Hypercholesterolemia (HoFH)

The combination of ZETIA and atorvastatin or simvastatin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Homozygous Sitosterolemia

ZETIA is indicated as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Therapy with lipid-altering agents should be a component of multiple risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to an appropriate diet (including restriction of saturated fat and cholesterol) and when the response to diet and other non-pharmacological measures has been inadequate. (See NCEP Adult Treatment Panel (ATP) III Guidelines, summarized in Table 7.)

Table 7
Summary of NCEP ATP III Guidelines

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes[a] (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents[b] (10-year risk >20%)[c]	<100	≥100	≥130 (100-129: drug optional)[d]
2+ Risk factors[e] (10-year risk ≤20%)[c]	<130	≥130	10-year risk 10-20%: ≥130[c] 10-year risk <10%: ≥160[c]
0-1 Risk factor[f]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[a] Therapeutic lifestyle changes include: 1) dietary changes: reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg per day), and enhancing LDL lowering with plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d), 2) weight reduction, and 3) increased physical activity.
[b] CHD risk equivalents comprise: diabetes, multiple risk factors that confer a 10-year risk for CHD >20%, and other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid artery disease).
[c] Risk assessment for determining the 10-year risk for developing CHD is carried out using the Framingham risk scoring. Refer to JAMA, May 16, 2001; 285 (19): 2486-2497, or the NCEP website (http://www.nhlbi.nih.gov) for more details.
[d] Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
[e] Major risk factors (exclusive of LDL cholesterol) that modify LDL goals include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on anti-hypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), age (men ≥45 years; women ≥55 years). HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.
[f] Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

Prior to initiating therapy with ZETIA, secondary causes for dyslipidemia (i.e., diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C [progestins, anabolic steroids, and corticosteroids]), should be excluded or, if appropriate, treated. A lipid profile should be performed to measure total-C, LDL-C, HDL-C and TG. For TG levels >400 mg/dL (>4.5 mmol/L), LDL-C concentrations should be determined by ultracentrifugation.

At the time of hospitalization for an acute coronary event, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

The combination of ZETIA with an HMG-CoA reductase inhibitor is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ZETIA is administered with an HMG-CoA reductase inhibitor in a woman of childbearing potential, refer to the pregnancy category and product labeling for the HMG-CoA reductase inhibitor. (See PRECAUTIONS, *Pregnancy*.)

PRECAUTIONS

Concurrent administration of ZETIA with a specific HMG-CoA reductase inhibitor should be in accordance with the product labeling for that HMG-CoA reductase inhibitor.

Liver Enzymes

In controlled clinical monotherapy studies, the incidence of consecutive elevations (≥3 X the upper limit of normal [ULN]) in serum transaminases was similar between ZETIA (0.5%) and placebo (0.3%).

In controlled clinical combination studies of ZETIA initiated concurrently with an HMG-CoA reductase inhibitor, the incidence of consecutive elevations (≥3 X ULN) in serum transaminases was 1.3% for patients treated with ZETIA administered with HMG-CoA reductase

inhibitors and 0.4% for patients treated with HMG-CoA reductase inhibitors alone. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. When ZETIA is co-administered with an HMG-CoA reductase inhibitor, liver function tests should be performed at initiation of therapy and according to the recommendations of the HMG-CoA reductase inhibitor.

Skeletal Muscle

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ZETIA compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 X ULN was 0.2% for ZETIA vs 0.1% for placebo, and 0.1% for ZETIA co-administered with an HMG-CoA reductase inhibitor vs 0.4% for HMG-CoA reductase inhibitors alone.

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients. (See CLINICAL PHARMACOLOGY, *Special Populations*.)

Drug Interactions (See also CLINICAL PHARMACOLOGY, *Drug Interactions*.)

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

Fibrates: The safety and effectiveness of ezetimibe administered with fibrates have not been established.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see ANIMAL PHARMACOLOGY). Co-administration of ZETIA with fibrates is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold.

HMG-CoA reductase inhibitors: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin.

Cyclosporine: The total ezetimibe level increased 12-fold in one renal transplant patient receiving multiple medications, including cyclosporine. Patients who take both ezetimibe and cyclosporine should be carefully monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on AUC_{2-4hr} for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on AUC_{2-4hr} for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on AUC_{2-4hr} for total ezetimibe).

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 times the human exposure at 10 mg daily based on AUC_{2-4hr} for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on AUC_{2-4hr} for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple dose studies of ezetimibe given in combination with HMG-CoA reductase inhibitors (statins) in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in combination therapy compared to monotherapy.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ZETIA is administered with an HMG-CoA reductase inhibitor to a woman of childbearing potential, refer to the pregnancy category and package labeling for the HMG-CoA reductase inhibitor. (See CONTRAINDICATIONS.)

Labor and Delivery

The effects of ZETIA on labor and delivery in pregnant women are unknown.

Nursing Mothers

In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe is excreted into human breast milk; therefore, ZETIA should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

Pediatric Use

The pharmacokinetics of ZETIA in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ZETIA in the pediatric population is limited to 4 patients (9 to 17 years) in the sitosterolemia study and 9 patients (11 to 17 years) in the HoFH study. Treatment with ZETIA in children (<10 years) is not recommended. (See CLINICAL PHARMACOLOGY, *Special Populations*.)

Geriatric Use

Of the patients who received ZETIA in clinical studies, 948 were 65 and older (this included 206 who were 75 and older). The effectiveness and safety of ZETIA were similar between these patients and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, *Special Populations*, and ADVERSE REACTIONS.)

ADVERSE REACTIONS

ZETIA has been evaluated for safety in more than 4700 patients in clinical trials. Clinical studies of ZETIA (administered alone or with an HMG-CoA reductase inhibitor) demonstrated that ZETIA was generally well tolerated. The overall incidence of adverse events reported with ZETIA was similar to that reported with placebo, and the discontinuation rate due to adverse events was also similar for ZETIA and placebo.

Monotherapy

Adverse experiences reported in ≥2% of patients treated with ZETIA and at an incidence greater than placebo in placebo-controlled studies of ZETIA, regardless of causality assessment, are shown in Table 8.

Table 8*
Clinical Adverse Events Occurring in ≥2% of Patients Treated with ZETIA and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Event	Placebo (%) n = 796	ZETIA 10 mg (%) n = 1681
Body as a whole – general disorders		
Fatigue	1.4	2.2
Gastro-intestinal system disorders		
Abdominal pain	2.8	3.0
Diarrhea	3.0	3.7
Infection and Infestations		
Infection viral	1.8	2.2
Pharyngitis	2.1	2.2
Sinusitis	2.6	2.6
Musculo-skeletal system disorders		
Arthralgia	3.4	3.8
Back pain	3.9	4.1
Respiratory system disorders		
Coughing	2.1	2.3

*Includes patients who received placebo or ZETIA doses reported in Table 9.

The frequency of less common adverse events was comparable between ZETIA and placebo.

Coinitiation with an HMG-CoA reductase inhibitor

ZETIA has been evaluated for safety in coinitiation studies in more than 2000 patients.

In general, adverse experiences were similar between ZETIA administered with HMG-CoA reductase inhibitors and HMG-CoA reductase inhibitors alone. However, the frequency of increased transaminases was slightly higher in patients receiving ZETIA administered with HMG-CoA reductase inhibitors than in patients treated with HMG-CoA reductase inhibitors alone. (See PRECAUTIONS, *Liver Enzymes*.)

Clinical adverse experiences reported in ≥2% of patients and at an incidence greater than placebo in four placebo-controlled trials where ZETIA was administered alone or initiated concurrently with various HMG-CoA reductase inhibitors, regardless of causality assessment, are shown in Table 9.

Table 9*
Clinical Adverse Events occurring in ≥2% of Patients and at an Incidence Greater than Placebo, Regardless of Causality, in ZETIA/Statin Coinitiation Studies

Body System/Organ Class Adverse Event	Placebo (%) n=259	ZETIA 10 mg (%) n=262	All Statins** (%) n=928	ZETIA + All Statins** (%) n=925
Body as a whole – general disorders				
Chest pain	1.2	3.4	2.0	1.9
Dizziness	1.2	2.7	1.4	1.8
Fatigue	1.5	1.9	1.4	2.8
Headache	6.4	8.9	7.3	6.5
Gastro-intestinal system disorders				
Abdominal pain	2.9	2.7	3.1	3.5
Diarrhea	1.5	3.4	2.9	2.8
Infection and Infestations				
Pharyngitis	1.9	3.1	2.5	2.3
Sinusitis	1.9	4.6	3.5	3.5
Upper respiratory tract infection	10.8	13.0	13.6	11.8
Musculo-skeletal system disorders				
Arthralgia	2.3	3.5	4.3	3.4
Back pain	3.5	3.4	3.7	4.3
Myalgia	1.9	3.0	4.1	4.5

*Includes four placebo-controlled coinitiation studies in which ZETIA was initiated concurrently with an HMG-CoA reductase inhibitor.

**No statins = all doses of all HMG-CoA reductase inhibitors.

OVERDOSAGE

No cases of overdosage with ZETIA have been reported. Administration of ezetimibe, 50 mg/day, to 15 subjects for up to 14 days was generally well tolerated. In the event of an overdose, symptomatic and supportive measures should be employed.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ZETIA and should continue on this diet during treatment with ZETIA.

The recommended dose of ZETIA is 10 mg once daily. ZETIA can be administered with or without food.

ZETIA may be administered with an HMG-CoA reductase inhibitor for incremental effect. For convenience, the daily dose of ZETIA may be taken at the same time as the HMG-CoA reductase inhibitor, according to the dosing recommendations for the HMG-CoA reductase inhibitor.

Patients with Hepatic Insufficiency

No dosage adjustment is necessary in patients with mild hepatic insufficiency (see PRECAUTIONS, *Hepatic Insufficiency*).

Patients with Renal Insufficiency

No dosage adjustment is necessary in patients with renal insufficiency (see CLINICAL PHARMACOLOGY, *Special Populations*).

Geriatric Patients

No dosage adjustment is necessary in geriatric patients (see CLINICAL PHARMACOLOGY, *Special Populations*).

Co-administration with Bile Acid Sequestrants

Dosing of ZETIA should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant (see PRECAUTIONS, *Drug Interactions*).

HOW SUPPLIED

No. 3881 - Tablets ZETIA, 10 mg, are white to off-white, capsule-shaped tablets debossed with "414" on one side. They are supplied as follows:

NDC 66582-414-31 bottles of 30
NDC 66582-414-54 bottles of 90
NDC 66582-414-74 bottles of 500
NDC 66582-414-28 unit dose packages of 100.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Protect from moisture.

MERCK / Schering-Plough Pharmaceuticals

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